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Biological and psychosocial evidence in the Cass Review: a critical commentary

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Abstract

Background

In 2020, the UK's National Health Services (NHS) commissioned an independent review to provide recommendations for the appropriate treatment for trans children and young people in its children's gender services. This review, named the Cass Review, was published in 2024 and aimed to provide such recommendations based on, among other sources, the current available literature and an independent research program.

Aim

This commentary seeks to investigate the robustness of the biological and psychosocial evidence the Review—and the independent research programme through it—provides for its recommendations.

Results

Several issues with the scientific substantiation are highlighted, calling into question the robustness of the evidence the Review bases its claims on.

Discussion

As a result, this also calls into question whether the Review is able to provide the evidence to substantiate its recommendations to deviate from the international standard of care for trans children and young people.

Keywords
gender identity, healthcare, policy, scientific rigor, transgender

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Introduction

The Cass Review (2024) is an independent review, commissioned in 2020 by the UK's National Health Services (NHS) to provide recommendations on children's gender services. The Review was commissioned in the context of particular hostility in the UK toward trans individuals (Walters et al., 2020), and a high-profile legal case regarding trans children's ability to consent to puberty blockers (de Vries et al., 2021). The review was written independent of the NHS gender services, and itself commissioned further independent systematic reviews, performed by scholars at the University of York. After an interim report published in 2022, The Review released its final findings in April 2024. In this final report, it aims to provide recommendations for a new standard of care for trans youth in the UK.

One of the central aims of the Cass Review is the "best available

collation of published evidence" (Cass, 2024, p. 52), and based on the collated evidence, provide scientifically substantiated recommendations. The Cass Review is based on 4 key sources, one of which, termed 'Evidence', forms the scientific basis of the Review. The evidence consists of a series of independent, peer-reviewed reviews, commissioned through the research programme, published in Archives of Disease in Childhood (Taylor et al., 2024a, 2024b, 2024c, 2024d), supplemented by additional qualitative and quantitative research throughout the Review. Among other topics, the Review discusses the biological and psychosocial evidence regarding the development of trans individuals and their brains, the effects of particular treatments, and how this may affect recommendations for healthcare for trans children and adolescents. Together, this evidence is used to substantiate the assertions which are used to support the key recommendations of the Review, notably several recommendations that deviate from the current international standard of care (SOC) as supported by the World Professional Association for Transgender Health (WPATH) (Coleman et al., 2022). As such, it is vital that the evidence is of high quality, and that its collection and collation follows standards of scientific rigor.

In this commentary, this scientific evidence is reviewed, particularly focusing on the biological and psychosocial claims reported in the Review. The scientific substantiation of assertions in the sections on understanding the patient cohort and clinical approaches is examined critically, resulting in the finding that the Review shows a number of issues that together point to a substandard level of scientific rigor in the Review. As such, it called in question whether the Review provides sufficient evidence to substantiate its recommendations to deviate from the international standard of care for trans children.

Changes in the patient profile

The Review first aims to understand the demographics of young people referred to gender services. To this end, a systematic review of the literature was commissioned. Taylor et al. (2024d) reviewed all English-language studies studying trans children and adolescents (<18yo) referred to gender or endocrinology services. The review includes data on referrals from 2000 until 2019, with varying coverage of this timeframe depending on the country. Based on this data, it notes both a sharp increase in overall referrals—in particular since 2014—and generally an increase in the percentage of individuals assigned female at birth. However, it is not clear whether these are statistically significant increases and what trend they follow over time. In addition, as the authors themselves points out, because of the low overall numbers in referrals, the ratio between those assigned female compared to male at birth tends to jump around for many countries included in the study (e.g. Scotland, Sweden, Germany). The authors conclude there is a "twofold to threefold increase in the number of referrals to specialist paediatric gender/endocrinology services over time across countries" (Taylor et al., 2024d, p. 6). However, it is unclear what timeframe this refers to specifically, and if this is based on the data corrected for population size, nor what the confidence interval is for the cited numbers.

The Cass Review further relies on a quantitative study of Clinical Practice Research Datalink (CPRD) data on gender dysphoria in the UK, which has not (yet) been published in a peer-reviewed journal, but is detailed in Appendix 5 of the Review (Cass, 2024). In this case, the authors claim a 100-fold increase, but do not include the precise numbers (prevalence in 2009 is cited as <0.1%) nor any statistics to support this claim. Although they provide 95% confidence intervals in their graphs, it is unclear what is used as the sample group to calculate these confidence intervals. The study does not discuss changes in confounds across the timeframe, such as changes in societal acceptance and diagnostic criteria across the measured timeframe (2009-2021), which may explain some of the

increases in prevalence. Lastly, the study does not provide an introduction detailing previous studies on the topic, or a conclusion placing the results into the larger context of the current scientific literature. Overall the study as written provides too little information to draw any statistically sound quantitative conclusions.

In addition to data about the sex assigned at birth, Taylor et al. (2024d) also explore the prevalence of comorbidities, specifically mental health disorders. Notably, they wrongly report the incidence of autism spectrum condition (ASC) as reported by Morandini et al. (2022), writing "[o]ne study reported data separately for 2012 and 2015 and demonstrated an increase from 1.8% to 15.1%" (Taylor et al., 2024d, p. 5), when the reported numbers were a non-significant increase from 13.8% to 15.1% ($p = .662$) (Morandini et al., 2022). Besides this study, no consistent co-occurrence of ASC and gender dysphoria is reported. In addition, when assessing ASC, two studies were included that only reported the scores on Items 9 and 66 on the Teacher's Report Form (TRF) (Zucker et al., 2017) or on the CBCL (VanderLaan et al., 2015), which measure obsessions and compulsions. If participants scored higher than a 0 (scale 0-2) on either behavior, they were included in the sample of ASC by Taylor et al. (2024d), along with the studies using clinical diagnoses. Thus, the conclusions on co-occurrence between ASC and gender dysphoria are unreliable.

The review by Taylor et al. (2024d) is used as a key source in the Cass Review's discussion on the prevalence of psychiatric disorders in young people referred to gender services, noting that "rates of depression, anxiety and eating disorders were higher in the gender clinic referred population than in the general population" (Cass, 2024, p. 91). However, as Taylor et al. (2024d) discuss, this data is based on varying measures. For example, across studies depression is measured using the Child Behavior Checklist (CBCL), DASS-21 (Depression, Anxiety and Stress Scale), DSM-5, Youth Self Report (YSR), BDI II (Beck Depression Inventory) and prior clinical diagnoses. Similar conflation of psychometric scales and medical

diagnoses is used across the other psychiatric disorders, as previously also demonstrated was the case for ASC. The vastly different criteria across these measures lead to a high variability across studies, and as such extreme caution should be taken when interpreting these results.

In further discussion of the prevalence of psychiatric disorders, the Cass Review claims in point 5.30 (p.91) that "[i]n Finland (Kaltiala-Heino et al., 2015; Karvonen et al., 2022) more than three-quarters of the referred adolescent population needed specialist child and adolescent psychiatric support due to problems other than gender dysphoria, many of which were severe, predated and were not considered to be secondary to the gender dysphoria." (Cass, 2024, p. 91). Kaltiala-Heino et al. (2015) reported 35/47 (74.5%) of the included participants had prior referrals for psychiatric treatment. They reported that 68% received these referrals prior to their first gender dysphoria treatment, however, no data is available about the referral time relative to gender dysphoria onset and the relative severity of these issues. Karvonen et al. (2022) report that 59.1% of adolescents received a psychiatric diagnosis. They also explicitly say that these disorders were not reported prior to gender dysphoria, and as such no causality can be inferred. Neither study supports the claim made in the Cass Report that more than three-quarters were referred for psychiatric issues other than gender dysphoria, or that the majority of these were severe and preceded gender dysphoria onset.

This section leads to a number of key recommendations (30-42). Notably, recommendation 31 (Cass, 2024, p. 26) states that "[a]mong referrals there is a greater complexity of presentation with high levels of neurodiversity and/or co-occurring mental health issues and a higher prevalence than in the general population of adverse childhood experiences and looked after children. The increase in referrals and change in case-mix is also being seen internationally". As demonstrated above, this claim is based on weak trends at best, with no clear support for increase in case-mix

or psychiatric disorders among the population (Karvonen et al., 2022). The Review further states in recommendation 35 (Cass, 2024, p.26): “the exponential change in referrals over a particularly short five-year timeframe is very much faster than would be expected for normal evolution of acceptance of a minority group”. It is not clear what the source is for the claim of an exponential change, as no trend analysis is performed on the data in Figure 15 of the Review (Cass, 2024). There is also no discussion on what the expected change based on evolution in acceptance would be, and how this is measured. In fact, in point 7.6 (Cass, 2024, p. 106), the Review reports an unprecedented evolution in acceptance of non-binary genders among generation Z, suggesting the trends around trans acceptance do not follow a normal evolution of acceptance of a minority group. Similar observations about an increase in overall numbers and a difference in the demographics of adolescents referred to gender services are also noted in the WPATH’s SOC (Coleman et al., 2022). However, this document discusses a number of reasons for these changes, including underestimation of numbers in previous studies, and changes to the sociopolitical landscape. Although some of the reasons are discussed by Cass (2024) in a later chapter, the Review fails to engage critically with the literature on this topic, for example by failing to discuss some of the key publications cited in the SOC.

Overall, the Review makes claims about trends in terms of demographics that are weakly substantiated, with no clear statistical basis for its quantitative discussion about exponential or two- to threefold increases. In addition, several sources are cited that do not support certain assertions, most notably those reporting trends in Finland. Furthermore, the Review shows internal inconsistencies, with seemingly contradictory reports on expected compared to unprecedented increases in acceptance of trans individuals. Lastly, despite difference in the conclusions between the Cass Review and the current SOC, the Review fails to critically engage in discussion of causes for such discrepancies.

Developmental considerations

The Review aims to find a biological basis of gender dysphoria, starting this section by stating that "[b]iological sex is determined by sex chromosomes" (Cass, 2024, p. 98). This is an oversimplification, as in the scientific literature there is no clear consensus about the exact meaning of 'biological sex' (Velocci, 2024). The Review goes on to discuss three "important ways in which sex differences are expressed" (Cass, 2024, p. 98): gender role behaviors, gender identity and sexual orientation (Babu & Shah, 2021). These three domains are used by studies looking at the psychosocial development of intersex individuals specifically, and it is unclear to what extent these domains would also apply to endosex individuals, i.e. those whose sex characteristics fit into the medical criteria of either male or female.

A central discussion point in this section of the Review relates to brain development. A main reference for the claims about brain development is a non-peer-reviewed article (Giedd, 2015). In the academic literature, the definition of a 'mature brain' is less clear, as the brain continually develops, grows and shrinks (Somerville, 2016; Tamnes et al., 2010). To highlight the importance of puberty and adolescence, the Review discusses the hypothesis of this time as a 'critical period' (Cass, 2024, p. 104), a theory put forward by Larsen and Luna (2018). However, while it seems the Review uses this term in its more colloquial meaning, the authors refer to a specific neurobiological phenomenon: a critical period is a time of increased plasticity when the neuronal network and its individual parts are particularly sensitive to incoming stimuli (Dehorter & Del Pino, 2020). In this meaning, there's not necessarily a clear link between brain maturation and the occurrence of a critical period during adolescence, nor is there clear consensus on the effect of hormones on neural circuits during a critical period. The only clear conclusion is—as the Cass Review rightfully notes—that more work is needed to understand these complex neurobiological interactions.

In summary, although puberty and adolescence are key times for brain development, claims about brain maturation are not as black-and-white as the Review posits. Additionally, the question as to how brain maturation should advise legal policies is a far-reaching one, beyond the scope of both this commentary and arguably the Cass Review, and should be considered with extreme caution (Somerville, 2016; Steinberg, 2009a, 2009b). The Cass Review provides insufficient evidence to claim that brain maturation should be a reason to prohibit or restrict gender care for children and adolescents, especially in the face of these far-reaching legal consequences for such a claim.

Growing up in the 2000s

Next, the Review discusses the societal background against which the current generation of trans children are growing up. A set of key points (7.16-7.20) poses a possible link between increased availability of sexually explicit materials and gender dysphoria, based on an article by Nadrowski (2024).[1] This article does not contain any primary research, but rather poses a yet untested theory. Indeed, the article itself notes that "no studies have yet directly linked exposure to pornography with gender dysphoria" (Nadrowski, 2024, p. 294). The argument in the Nadrowski paper is not supported by data, and as the only source, is not sufficient to suggest a link between pornography and gender dysphoria.

In point 7.28, the Review states that "[t]he increase in presentations to gender clinics has to some degree paralleled this deterioration in child and adolescent mental health" (Cass, 2024, p. 111), based solely on the fact that both have gone up in recent years. The Review seems to imply causation here, but since the causes of these increases is poorly understood, it is highly possible either a confound is present that would explain both increases, or that an increased number of children with gender dysphoria is impacted by societal pressure and hostility, leading to the increase

in mental health problems. Indeed, the WPATH SOC stresses the effects of this "minority stress" on trans individuals in particular (Testa et al., 2015), leading to mental health disparities (Coleman et al., 2022), which is dismissed by Cass (2024) in point 8.41 and 8.42 without clear reason. The Cass Review further state that "[m]any young people with gender dysphoria are presenting with combinations of the above conditions" (Cass, 2024, p.112). No source is given for this statement here, so it is unclear how this compares to the overall population, and whether and statistically significant trends are present.

Overall, although this section discusses a number of important societal developments that may increasingly impact young people, it fails to engage critical with established theories on causes of mental health issues in trans youth, in particular the effects of minority stress. In addition the Review fails to provide any concrete evidence of causal links between the societal factors affecting the younger generation they discuss and increases in gender dysphoria.

Possible factors influencing the change in patient profile

In exploring the factors causing changes in patient profiles, the Review asserts that "[f]or many centuries transgender people have been predominantly trans females" (Cass, 2024, p. 114). It is unclear what evidence supports this statement. Studying the prevalence of transgender people and their identity has been made difficult by the continued criminalization of trans identities and the destruction of historical materials, for example when the Institut für Sexualwissenschaft was destroyed in Nazi Germany (Aghi et al., 2024). Despite this, many accounts of 'women' living as men, who may call themselves transmasculine or trans men in today's world, have been reported across history (Hager, 2018; Skidmore, 2017). In addition, genders outside of the strict binary have historically exists,

and still do, across the world, such the various gender identities within Indigenous nations in North America (Robinson, 2019). The assumption that trans history was dominated by trans women primes the idea of a shifting patient profile, but there is no evidence to support this assertion.

In its discussion of the effects of hormone exposure on brain structure, the Review cites Ristori et al. (2020), to support the statement that "[t]here is evidence that masculinizing/feminizing hormone treatments alter brain structure" (Cass, 2024, p. 116). Within the paper by Ristori et al. (2020), three primary sources are cited for this claim (Pol et al., 2006; Rametti et al., 2012; Zubiaurre-Elorza et al., 2014). These studies into the effect of cross-sex hormones on the brains of trans individuals—all performed on cohorts with an average age of 25-30, not during puberty—indeed show changes in volume, cortical thickness, and white matter structure after hormone treatment. However, one should consider that brain structure naturally changes over time, and may be affected by endogenous hormones as well. Therefore, a proper matched control—which matches both in overall hormone levels and demographics—would be needed to conclusively say that masculinizing or feminizing hormone treatments alter brain structure.

Two of the three studies (Rametti et al., 2012; Zubiaurre-Elorza et al., 2014) discussed by Ristori et al. (2020) report differences in brain structure in trans individuals prior to the onset of hormone treatment. Indeed, the review later (point 8.19) cites Mueller et al. (2021), who also find differences between (non-hormonally treated) trans and cis individuals. The Review dismisses this paper saying it claims the "equivalent to suggesting that all neurodiverse people had the same unique brain" (Cass, 2024, p. 116). However, this is a misinterpretation of the claims by Mueller et al. (2021), who argue that the overall patterns of anatomy are statistically different between the four different groups (trans and cis men and women), rather than falling into two categories of 'male' and 'female'. Having

dismissed this study, the Review claims “research in this area has not reliably identified brain changes directly linked to gender incongruence” (Cass, 2024, p. 116). Although a thorough review is needed to determine how reliable these brain changes are, three independent studies, two of which are primary sources to support another statement, show evidence of changes linked to gender incongruence, suggesting there is evidence available that people with gender dysphoria show differences in their brain structure.

In point 8.14, the Review cites Karamanis et al. (2022) as a large register-based population study, to show that trans identity is mainly determined by environmental factors, rather than having a genetic basis. However, this study included only 67 twins, and as such is much smaller than the numerous other studies (Alanko et al., 2010; Bailey et al., 2000; Burri et al., 2011; Sasaki et al., 2016; Van Beijsterveldt et al., 2006) which did find support for heritability of trans identity. The Review does not discuss or cite any of these other studies, or explain why the Karamanis study was determined to be the most relevant. The Review argues that this study gives more credence to the idea of sex hormone exposure in the womb causing gender dysphoria. However, given the numerous contradictory findings in the literature, this single study does not provide sufficient evidence to give due credence.

Next, the Review poses that “ACEs [Adverse Childhood Events] are a predisposing factor” (8.40) for gender dysphoria (Cass, 2024, p.119). Although Taylor et al. (2024d) report incidences of ACEs in trans youth, they do not provide evidence of it being a predisposing factor. Similarly, Di Ceglie (2002) reports incidences, but fails to include a control group, thus making it unclear whether the prevalence in trans individuals is significantly increased. Neither study is able to prove causality, as by the time of the assessment, the individuals had already presented with gender dysphoria. It is therefore possible that the ACEs are a consequence of gender dysphoria (e.g. when a child starts presenting gender divergent behavior, this may cause the parent to start abusing the child). To

assert that something is a predisposing factor, a causal relationship should be demonstrable, which is not the case with ACEs and gender dysphoria.

Overall, this section discussing possible factors which have influenced the patient profile shows several issues in providing evidence to substantiate its claims. For several key assertion, single studies are cited when a wealth of contradictory studies are available, showing a lack of balanced consideration of the literature. This calls into question the robustness of the listed conclusions of this section (8.52-8.62), and any recommendations the Review makes based on these.

Clinical approach & clinical management

The section on clinical approach and clinical management discusses current practices for the treatment of trans youth, which is outside of the scope of this commentary. However, two key recommendations depend on scientific evidence: administration of puberty blockers and hormone therapy. The Review recommends the provision of puberty blockers only under a research protocol, which contradicts the WPATH SOC, which recommends puberty blockers for any adolescent who meets the outlined criteria and who has reached Tanner stage 2. The Review argues not enough evidence is available to justify the use of puberty blockers, given the risks perceived by the writers. Cass (2024) further recommends a minimum age of 18 for the administration of hormone therapy, whereas the WPATH SOC does not indicate a minimum age, but argues providing hormone therapy prior to the previous recommended age of 16 may be beneficial. The recommendations in the Cass Review are largely based on two commissioned reviews (Taylor et al., 2024a; 2024b), discussed below, as well as supplemental literature cited throughout the Review.

Taylor et al. (2024a) identified 50 papers of the effects of puberty blockers on physiological, psychosocial, gender dysphoria

and physical health outcomes. Only one cross-sectional study was marked as high-quality, and 25 as moderate-quality, the remaining studies were excluded from analysis. Although the authors argue no clear conclusions could be drawn about psychosocial outcomes, of the four studies included, none showed negative effects within the first year. The only study showing decreased cognitive functioning, was potentially confounded by other treatments (such as cross-sex hormones). However, despite finding mixed results for height outcome—with three out of seven studies seeing no decrease in growth—the authors do conclude based on this evidence that "gains in height may lag behind that seen in other adolescents" (Taylor et al., 2024a, p. 12). This conclusion is subsequently listed in the Review as a risk of puberty blockers (point 14.43). However, the Review contradicts this finding itself, reporting in point 14.32 that "[e]vidence to date suggests that puberty blockers [does not] lead to substantially reduced adult height in transgender females" (Cass, 2024, p. 177). It is unclear based on what standards of proof either claim is made, and why two contradictory assertions are made within the Review.

When further discussing the results reported by Taylor, Mitchell, Hall, Heathcote, et al., the Review notes that vaginoplasty may be more difficult in trans women treated earlier in puberty with puberty blockers (14.41), which was reported in at least two studies (Lee et al., 2023; van de Grift et al., 2020). However, both studies note that those assigned female at birth are less likely to require a mastectomy, and if they do the surgery is less invasive, when they receive puberty suppression earlier. This is not discussed in the Review, and not considered in its recommendations on when to start puberty blockers for these individuals.

In a second review by Taylor et al. (2024b) 53 studies on hormone treatment were analyzed, with again only one marked as high-quality. Overall, the review surmises that no conclusions can be drawn regarding the effects of hormone treatment, due to inconsistent evidence and lack of quality of the studies, which is

reported in the Cass Review. However, in a prior point arguing against the use of puberty blockers in trans men (14.56), the Review argues that "transgender males masculinize well on testosterone" (Cass, 2024, p. 180), which is in direct contradiction with this previous conclusion. Taylor et al. (2024b) further concluded there was no clear effect of hormone treatment on suicidality in trans individuals, despite three out of four papers showing a reduction in suicidality after hormone treatment. In addition to the papers included in this review, which examined studies up to April 2022, the Cass Review discusses several papers showing a reduction in suicidality (15.36-15.43), but—like Taylor et al. (2024b)—concludes the results to be too inconsistent.

Overall, the Cass Review generally cautions against drawing any conclusions about the positive effects of puberty blockers and hormone treatments, for example regarding improvements in psychosocial outcomes and suicidality. However, based on the same studies and similar quality evidence, the Review cautions against the potential negative outcomes, such as the effect of puberty blockers on adult height or vaginoplasty outcomes. Across the topics of puberty blockers and hormone treatment, neither the Cass review, or the commissioned reviews, give a clear definition of when results are deemed too inconsistent. Indeed, it seems like varying thresholds are employed throughout the texts. Ultimately Cass (2024) provides the recommendations of prescribing puberty blockers only on a research protocol, and not providing hormone therapy before the age of 18, which both critically deviate from the current SOC. This difference in recommendation seems to stem from the risks perceived by Cass (2024), which, as shown, are poorly evidenced, and are not of sufficient quality to warrant deviation from the SOC.

Detransition

Within the context of hormone treatment, the Review discusses

detransitioners, people who have transitioned previously, but reverted to the gender matching their sex assigned at birth. In discussing the reasons for detransitioning, a main source cited is a study by Littman (2021). Notably, Littman previously published a study on gender dysphoria in adolescents (Littman, 2018). This study was subsequently widely criticized for its flawed methodology (Ashley, 2020; Restar, 2020), leading to a substantial correction of the original manuscript (Littman, 2019). Littman's work should therefore be considered with increased scrutiny, in particular regarding whether the methodology used to obtain the results is robust. Indeed, the cited study (Littman, 2021), as well as the second study cited in the Review (Vandenbussche, 2022) while discussing reasons for detransitioning, has similar methodological issues to the previous study: potentially biased recruitment practices. In both studies, participants were particularly recruited from online detransition-related groups, potentially artificially inflating the number of people with negative views about transitioning and gender affirmative care. These studies found that realizing their gender dysphoria had other causes was the main reason for detransitioning. In contrast, Turban et al. (2021) recruited participants from a large cohort of people who had filled out the Transgender Survey, and found that the most prominent reasons of detransitioning was pressure from parents or societal pressures. This study may also include a recruitment bias, for example, detransitioners may no longer identify as transgender, and therefore not fill out the Transgender Survey. However, given the issues with the two referenced studies, it would be appropriate to additionally discuss this much larger study to provide a balanced overview of the literature. In failing to do so, the Cass Review presents a flawed and unbalanced view, leading to potentially misrepresenting the major causes of detransition, and as such the type of support this population benefits from most. In particular, the Review posits other issues causing the gender dysphoria as the main cause for detransitioning, priming the recommendation that treating

other issues—such as mental health issues—prior to providing gender-affirming care may reduce detransition rates. However, this recommendation would not be appropriate based on the reasons reported by Turban et al. (2021), who find external factors to be the major cause for detransitioning. In this case, increasing support and acceptance, both clinical and societal, is likely more effective at reducing detransitioning rates, and focussing on other issues prior to gender-affirming care may ultimately lead to worse clinical outcomes.

Discussion

Overall, this commentary highlights numerous of issues with the scientific substantiation of the biological and psychosocial claims made by the Cass Review. Where quantitative data is referenced or included, statistical measures are missing for claims about trends and differences between groups. In addition, in several claims a balanced discussion of the available literature lacks, and varying standards for quality of evidence are used throughout the Review. In addition, the Review makes a number of contradictory assertions. These issues point toward poor scientific rigor in the evidence collation and dissemination, leading to potentially wrong conclusions and recommendations.

Although the current commentary focuses on the biological and psychosocial evidence presented in the Cass Review, other issues with the Review and its process have previously been raised (Horton, 2024). This article raises a number of similar concerns discussed here, in particular inconsistent standards of evidence. However, further concerns regarding prejudice and a cisnormative bias are also examined. Although science claims to be fully impartial, it never exists in a vacuum, and the confounding factors discussed by Horton should be considered carefully when interpreting the Review.

One of the central recommendations of the Review is the

discontinuation of puberty blockers as standard practice for trans children within the NHS. As this is in direct conflict with long-standing international standards of care (Taylor et al., 2024c), it would be expected this recommendation is supported by substantial question about its positive effects of puberty blockers, and/or overwhelming evidence of their adverse effects. Such evidence is not presented in the Cass Review. Similarly, the Review argues there is insufficient evidence of long-term positive effects of hormone treatment in adolescents, recommending against early treatments, again directly contradicting international standards, and the large number of studies used to develop these standards.

All in all, this commentary raises numerous concerns regarding the biological and psychosocial evidence in the Cass Review. These concerns include inferring trends and causality about demographic trends and comorbidities within statistical substantiation, misrepresenting results from the literature, varying thresholds for the inclusion of studies and using unbalanced evidence or references to make one-sided claims. Together, these concerns call into question whether the Review is able to provide sufficient evidence to substantiate its recommendations to deviate from WPATH's international standard of care for trans children (Coleman et al., 2022).

Notes

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References

Aghi, K., Anderson, B. M., Castellano, B. M., Cunningham, A., Delano, M., Dickinson, E. S., von Diezmann, L., Forslund-Startceva, S. K., Grijseels, D. M., Groh, S. S., Guthman, E. M., Jayasinghe, I., Johnston, J., Long, S., McLaughlin, J. F., McLaughlin, M., Miyagi, M., Rajaraman, B., Sancheznieto, F., … Weinberg, Z. Y. (2024). Rigorous science demands support of transgender scientists. *Cell*, *187*(6), 1327–1334. Crossref. PubMed. Web of Science.

Alanko, K., Santtila, P., Harlaar, N., Witting, K., Varjonen, M., Jern, P., Johansson, A., von der Pahlen, B., & Sandnabba, N. K. (2010). Common genetic effects of gender atypical behavior in childhood and sexual orientation in adulthood: A study of Finnish twins. *Archives of Sexual Behavior*, *39*(1), 81–92. Crossref. PubMed. Web of Science.

Ashley, F. (2020). A critical commentary on 'rapid-onset gender dysphoria'. *The Sociological Review*, *68*(4), 779–799. Crossref. Web of Science.

Babu, R., & Shah, U. (2021). Gender identity disorder (GID) in adolescents and adults with differences of sex development (DSD): A systematic review and meta-analysis. *Journal of Pediatric Urology*, *17*(1), 39–47. Crossref. PubMed. Web of Science.

Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. *Journal of Personality and Social Psychology*, *78*(3), 524–536. Crossref. PubMed. Web of Science.

Burri, A., Cherkas, L., Spector, T., & Rahman, Q. (2011). Genetic and environmental influences on female sexual orientation, childhood gender typicality and adult gender identity. *PloS One*, *6*(7), e21982. Crossref. PubMed. Web of Science.

Cass, H. (2024). The Cass Review. https://cass.independent-review.uk/home/publications/final-report/

Coleman, E., Radix, A. E., Bouman, W. P., Brown, G. R., de Vries, A. L.

C., Deutsch, M. B., Ettner, R., Fraser, L., Goodman, M., Green, J., Hancock, A. B., Johnson, T. W., Karasic, D. H., Knudson, G. A., Leibowitz, S. F., Meyer-Bahlburg, H. F. L., Monstrey, S. J., Motmans, J., Nahata, L., … Arcelus, J. (2022). Standards of care for the health of transgender and gender diverse people, version 8. *International Journal of Transgender Health*, *23*(Suppl 1), S1–S259. Crossref. PubMed. Web of Science.

de Vries, A. L., Richards, C., Tishelman, A. C., Motmans, J., Hannema, S. E., Green, J., & Rosenthal, S. M. (2021). Bell v Tavistock and Portman NHS Foundation Trust [2020] EWHC 3274: Weighing current knowledge and uncertainties in decisions about gender-related treatment for transgender adolescents. *International Journal of Transgender Health*, *22*(3), 217–224. Crossref. PubMed. Web of Science.

Dehorter, N., & Del Pino, I. (2020). Shifting developmental trajectories during critical periods of brain formation. *Frontiers in Cellular Neuroscience*, *14*, 283. Crossref. PubMed. Web of Science.

Di Ceglie, D., Freedman, D., McPherson, S., & Richardson, P. (2002). Children and adolescents referred to a specialist gender identity development service: Clinical features and demographic characteristics. *International Journal of Transgenderism, 6*(1), 97–103.

Giedd, J. N. (2015). The amazing teen brain. *Scientific American*, *312*(6), 32–37. Crossref. PubMed. Web of Science.

Hager, L. (2018). A case for a trans studies turn in Victorian studies. *Victorian Review*, *44*(1), 37–54. Crossref.

Horton, C. (2024). The Cass review: Cis-supremacy in the UK's approach to healthcare for trans children. *International Journal of Transgender Health*, 1–25. Advance online publication. Crossref. PubMed. Web of Science.

Kaltiala-Heino, R., Sumia, M., Työläjärvi, M., & Lindberg, N. (2015). Two years of gender identity service for minors: Overrepresentation of natal girls with severe problems in adolescent development. *Child and Adolescent Psychiatry and Mental Health*, *9*(1), 9. Crossref. PubMed. Web of Science.

Karamanis, G., Karalexi, M., White, R., Frisell, T., Isaksson, J., Skalkidou, A., & Papadopoulos, F. C. (2022). Gender dysphoria in twins: A register-based population study. *Scientific Reports*, *12*(1), 13439. Crossref. PubMed. Web of Science.

Karvonen, M., Karukivi, M., Kronström, K., & Kaltiala, R. (2022). The nature of co-morbid psychopathology in adolescents with gender dysphoria. *Psychiatry Research*, *317*, 114896. Crossref. PubMed. Web of Science.

Larsen, B., & Luna, B. (2018). Adolescence as a neurobiological critical period for the development of higher-order cognition. *Neuroscience*

& Biobehavioral Reviews, *94*, 179–195. Crossref. PubMed. Web of Science.
Lee, W. G., Butler, G., Carmichael, P., Rashid, T., Yasmin, E., Morley, R., Barrett, J., Christopher, N., & Sangster, P. (2023). Urological and gynaecological considerations for the use of gonadotropin-releasing hormone analogues in transgender and nonbinary adolescents: A narrative review. *European Urology Focus*, *9*(1), 35–41. Crossref. PubMed.
Littman, L. (2018). Rapid-onset gender dysphoria in adolescents and young adults: A study of parental reports. *PloS One*, *13*(8), e0202330. Crossref. PubMed. Web of Science.
Littman, L. (2019). Correction: Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. *PloS One*, *14*(3), e0214157. Crossref. PubMed. Web of Science.
Littman, L. (2021). Individuals treated for gender dysphoria with medical and/or surgical transition who subsequently detransitioned: A survey of 100 detransitioners. *Archives of Sexual Behavior*, *50*(8), 3353–3369. Crossref. PubMed. Web of Science.
Morandini, J. S., Kelly, A., de Graaf, N. M., Carmichael, P., & Dar-Nimrod, I. (2022). Shifts in demographics and mental health co-morbidities among gender dysphoric youth referred to a specialist gender dysphoria service. *Clinical Child Psychology and Psychiatry*, *27*(2), 480–491. Crossref. PubMed. Web of Science.
Mueller, S. C., Guillamon, A., Zubiaurre-Elorza, L., Junque, C., Gomez-Gil, E., Uribe, C., Khorashad, B. S., Khazai, B., Talaei, A., Habel, U., Votinov, M., Derntl, B., Lanzenberger, R., Seiger, R., Kranz, G. S., Kreukels, B. P. C., Kettenis, P. T. C., Burke, S. M., Lambalk, N. B., … Luders, E. (2021). The neuroanatomy of transgender identity: Mega-analytic findings from the ENIGMA transgender persons working group. *The Journal of Sexual Medicine*, *18*(6), 1122–1129. Crossref. PubMed. Web of Science.
Nadrowski, K. (2024). A new flight from womanhood? The importance of working through experiences related to exposure to pornographic content in girls affected by gender dysphoria. *Journal of Sex & Marital Therapy*, *50*(3), 293–302. Crossref. PubMed. Web of Science.
Pol, H. E. H., Cohen-Kettenis, P. T., Van Haren, N. E., Peper, J. S., Brans, R. G., Cahn, W., Schnack, H. G., Gooren, L. J., & Kahn, R. S. (2006). Changing your sex changes your brain: Influences of testosterone and estrogen on adult human brain structure. *European Journal of Endocrinology*, *155*(suppl_1), S107–S114. Crossref. Web of Science.
Rametti, G., Carrillo, B., Gómez-Gil, E., Junque, C., Zubiaurre-Elorza, L., Segovia, S., Gomez, Á., Karadi, K., & Guillamon, A. (2012). Effects of androgenization on the white matter microstructure of female-to-male transsexuals. A diffusion tensor imaging study.

Psychoneuroendocrinology, *37*(8), 1261–1269. Crossref. PubMed. Web of Science.
Restar, A. J. (2020). Methodological critique of Littman's (2018) parental-respondents accounts of "rapid-onset gender dysphoria. *Archives of Sexual Behavior*, *49*(1), 61–66. Crossref. PubMed. Web of Science.
Ristori, J., Cocchetti, C., Romani, A., Mazzoli, F., Vignozzi, L., Maggi, M., & Fisher, A. D. (2020). Brain sex differences related to gender identity development: Genes or hormones? *International Journal of Molecular Sciences*, *21*(6), 2123. Crossref. PubMed. Web of Science.
Robinson, M. (2019). Two-spirit identity in a time of gender fluidity. *Journal of Homosexuality*, *67*(12), 1675–1690. Crossref. PubMed. Web of Science.
Sasaki, S., Ozaki, K., Yamagata, S., Takahashi, Y., Shikishima, C., Kornacki, T., Nonaka, K., & Ando, J. (2016). Genetic and environmental influences on traits of gender identity disorder: A study of Japanese twins across developmental stages. *Archives of Sexual Behavior*, *45*(7), 1681–1695. Crossref. PubMed. Web of Science.
Skidmore, E. (2017). True sex: The lives of trans men at the turn of the twentieth century. In *True sex*. New York University Press. Crossref.
Somerville, L. H. (2016). Searching for signatures of brain maturity: What are we searching for? *Neuron*, *92*(6), 1164–1167. Crossref. PubMed. Web of Science.
Steinberg, L. (2009a). Adolescent development and juvenile justice. *Annual Review of Clinical Psychology*, *5*(1), 459–485. Crossref. PubMed. Web of Science.
Steinberg, L. (2009b). Should the science of adolescent brain development inform public policy? *The American Psychologist*, *64*(8), 739–750. Crossref. PubMed. Web of Science.
Tamnes, C. K., Østby, Y., Fjell, A. M., Westlye, L. T., Due-Tønnessen, P., & Walhovd, K. B. (2010). Brain maturation in adolescence and young adulthood: Regional age-related changes in cortical thickness and white matter volume and microstructure. *Cerebral Cortex*, *20*(3), 534–548. Crossref. PubMed. Web of Science.
Taylor, J., Mitchell, A., Hall, R., Heathcote, C., Langton, T., Fraser, L., & Hewitt, C. E. (2024a). Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*. Advance online publication. Crossref. Web of Science.
Taylor, J., Mitchell, A., Hall, R., Langton, T., Fraser, L., & Hewitt, C. E. (2024b). Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*. Advance online

publication. Crossref. Web of Science.
Taylor, J., Hall, R., Heathcote, C., Hewitt, C. E., Langton, T., & Fraser, L. (2024c). Clinical guidelines for children and adolescents experiencing gender dysphoria or incongruence: A systematic review of guideline quality (part 1). *Archives of Disease in Childhood*. Advance online publication. Crossref. Web of Science.
Taylor, J., Hall, R., Langton, T., Fraser, L., & Hewitt, C. E. (2024d). Characteristics of children and adolescents referred to specialist gender services: A systematic review. *Archives of Disease in Childhood*. Advance online publication. Crossref. Web of Science.
Testa, R. J., Habarth, J., Peta, J., Balsam, K., & Bockting, W. (2015). Development of the gender minority stress and resilience measure. *Psychology of Sexual Orientation and Gender Diversity*, *2*(1), 65–77. Crossref.
Turban, J. L., Loo, S. S., Almazan, A. N., & Keuroghlian, A. S. (2021). Factors leading to "detransition" among transgender and gender diverse people in the United States: A mixed-methods analysis. *LGBT Health*, *8*(4), 273–280. Crossref. PubMed. Web of Science.
Van Beijsterveldt, C., Hudziak, J. J., & Boomsma, D. I. (2006). Genetic and environmental influences on cross-gender behavior and relation to behavior problems: A study of Dutch twins at ages 7 and 10 years. *Archives of Sexual Behavior*, *35*(6), 647–658. Crossref. PubMed. Web of Science.
van de Grift, T. C., van Gelder, Z. J., Mullender, M. G., Steensma, T. D., de Vries, A. L., & Bouman, M.-B. (2020). Timing of puberty suppression and surgical options for transgender youth. *Pediatrics*, *146*(5), Article e20193653. Crossref. PubMed. Web of Science.
Vandenbussche, E. (2022). Detransition-related needs and support: A cross-sectional online survey. *Journal of Homosexuality*, *69*(9), 1602–1620. Crossref. PubMed. Web of Science.
VanderLaan, D. P., Postema, L., Wood, H., Singh, D., Fantus, S., Hyun, J., Leef, J., Bradley, S. J., & Zucker, K. J. (2015). Do children with gender dysphoria have intense/obsessional interests? *Journal of Sex Research*, *52*(2), 213–219. Crossref. PubMed. Web of Science.
Velocci, B. (2024). The history of sex research: Is "sex" a useful category? *Cell*, *187*(6), 1343–1346. Crossref. PubMed. Web of Science.
Walters, M. A., Paterson, J., Brown, R., & McDonnell, L. (2020). Hate crimes against trans people: Assessing emotions, behaviors, and attitudes toward criminal justice agencies. *Journal of Interpersonal Violence*, *35*(21-22), 4583–4613. Crossref. PubMed. Web of Science.
Zubiaurre-Elorza, L., Junque, C., Gómez-Gil, E., & Guillamon, A. (2014). Effects of cross-sex hormone treatment on cortical thickness in transsexual individuals. *The Journal of Sexual Medicine*, *11*(5), 1248–

1261. Crossref. PubMed. Web of Science.
Zucker, K. J., Nabbijohn, A. N., Santarossa, A., Wood, H., Bradley, S. J., Matthews, J., & VanderLaan, D. P. (2017). Intense/obsessional interests in children with gender dysphoria: A cross-validation study using the Teacher's Report Form. *Child and Adolescent Psychiatry and Mental Health*, *11*(1), 51. Crossref. PubMed. Web of Science.

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